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Using Triethynylphosphine Ligands Bearing Bulky End Caps To Create a Holey Catalytic Environment: Application to Gold(I)-Catalyzed Alkyne Cyclizations

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Triethynylphosphines are an interesting class of compounds that can be used as phosphorus ligands in transition metal complexes.[1] Owing to the linearity of the sp-hybridized carbon atoms, triethynylphosphines possess a rigid tripodal framework with the minimum steric demand around the phosphorus center. The entire structure can be varied through the substituents at the alkyne termini without affecting the steric environment in proximity to the phosphorus center. Despite these intriguing characteristics, however, no catalytic application of triethynylphosphines has been reported. This seems to be due to the reactivity of the alkyne sites[2] and the complexity of the coordination modes.[3] We envisioned that bulky substituents at the alkyne termini could protect the alkyne sites from approach by a metal, thus enabling the use of this class of compounds as η^1-coordinating phosphorus ligands.

Here we report the synthesis, properties and catalytic uses of phosphinoalkynes bearing bulky end caps at the alkyne termini, that is, tris[(triarylsilyl)ethynyl]phosphines (**1a**,**b**). The most salient feature of the new phosphines is the holey molecular shape possessing a deep and large-scale metal-binding cavity.[4] The holey phosphines displayed remarkable rate enhancement in the gold(I)-catalyzed[5] six- and seven-membered ring forming cyclizations of acetylenic keto esters[6] and 1,7-enynes.[7] We propose that the cavity in the ligand forces a nucleophilic center (enol or alkene) of the acetylenic compounds close to the gold-bound alkyne.

Phosphines **1a**,**b** were prepared from the corresponding aryl bromides through a two-step procedure in 72 and 67% overall yields, respectively (Scheme 1).[8] The compounds are stable against air oxidation not only in crystal form but also in solution.

We conceived that the holey catalytic environments created in **1a**,**b** might be advantageous for cyclization reactions and decided to apply them to a gold(I)-catalyzed alkyne cyclization. Reaction of triethynylphosphines **1a**,**b** with an equimolar amount of AuCl·SMe_2 formed neutral complexes [AuCl(**1**)]. The ^{31}P and ^{13}C NMR results confirmed that the ethynylphosphines are η^1-P-coordinated, leaving the alkyne moieties free from coordination. The neutral gold(I) complexes were converted to a cationic form (**2a**,**b**) by treatment with excess Ag[$N(SO_2CF_3)_2$], and a filtered solution was applied to the alkyne cyclizations.[6c]

We found that triethynylphosphine **1a** shows a marked advantage over conventional phosphine ligands when applied to the gold(I)-catalyzed 6-*exo*-*dig* cyclization of acetylenic keto ester **3a** (Table 1, entries 1−6). It should be noted that the gold(I)-catalyzed 6-*exo*-*dig* cyclization of simple acetylenic keto esters leading to monocyclic methylenecyclohexane derivatives has not been described in the literature,[9] whereas many examples of the 5-*exo*-*dig* and 5-*endo*-*dig* cyclizations have been reported.[5] Thus, treatment of **3a** with a CH_2Cl_2 solution containing 1 mol % cationic gold(I) complex **2a** resulted in smooth conversion at room temperature, the reaction being completed within 1.5 h to afford **4a** in quantitative yield (entry 1). In contrast, there was almost no reaction with the corresponding PPh_3 complex (3%, 1.5 h, entry 2). Bulky, biphenyl-based phosphines such as **5a**,**b**,[10] which were reported to be exquisite ligands in the gold-catalyzed reactions of 1,6-enynes, failed to activate the gold catalyst in promotion of the present reaction (entries 3 and 4). The complex formed with the $P(OPh)_3$ ligand, whose donor power is estimated to be comparable with the triethynylphosphines,[11] catalyzed the cyclization with much lower efficiency (21%, 6 h, entry 5) than that achieved with **1a**. The existence of a bulky substituent in triarylphosphite **6** had only a little influence on the activity of the gold catalyst (entry 6).

Comparison of triethynylphosphines (**1a**-**d**) bearing silicon end caps with varying steric demands and shapes indicated that a ligand steric factor is crucial for promotion of the cyclization. Phosphine **1b**, which has 3,5-$(Me_3Si)_2$-C_6H_3 terminal *Si*-aryl groups instead of the 3,5-(*t*-Bu)$_2$-4-MeO-C_6H_2 groups in **1a**, was also effective in conversion of **3a** to **4a**, but its gold complex (**2b**) showed apparently lower catalytic activity than **2a**, achieving only 70% conversion after 5 h (Table 1, entry 7). Upon removal of the meta substituents on the terminal Ar_3Si groups, the activity of the gold complexes disappeared almost completely (**1c**, 4% conversion, 2.5 h) (entry 8). The ligand with Si(*i*-Pr)$_3$ end caps (**1d**), whose steric demand is fairly large in the vicinity of the ligand alkyne moiety but is too small to reach to the reaction site, showed again some

Scheme 1

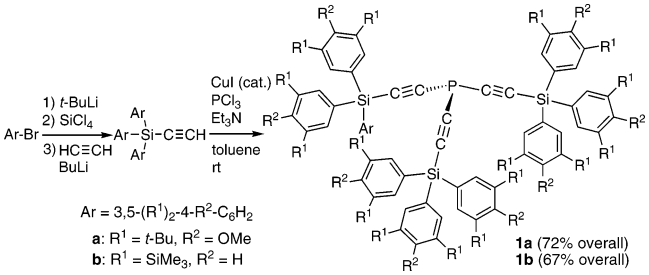
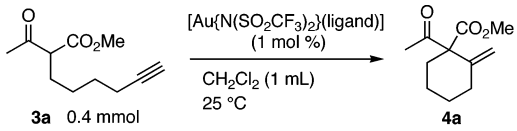
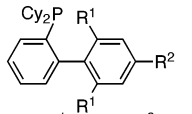


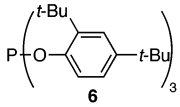
Table 1. Gold(I)-Catalyzed 6-*exo*-*dig* Cyclization of **3a**



entry	ligand	time, h	yield, % (^{1}H NMR)
1	**1a**	1.5	100
2	PPh_3	1.5	3
3	**5a**	1.5	<1
4	**5b**	1.5	<1
5	$P(OPh)_3$	6	21
6	**6**	6	28
7	**1b**	5	70
8	**1c**	2.5	4
9	**1d**	1.5	13



5a: R^1 = OMe, R^2 = H
5b: R^1 = R^2 = *i*-Pr



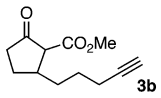
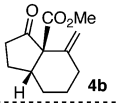
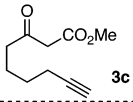
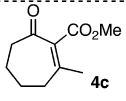
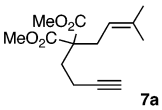
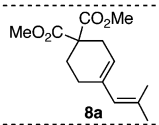
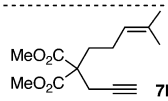
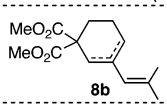
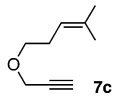
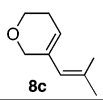
6

1c: P(C≡C−SiPh$_3$)$_3$

1d: P(C≡C−Si(*i*-Pr)$_3$)$_3$

10.1021/ja066800c CCC: $33.50

Table 2. Cyclization of Various Acetylenic Compounds Catalyzed by the Cationic Gold(I) Complex [Au{N(SO_2CF_3)$_2$}(Ligand)].[a]

entry	alkyne	product	ligand	time	isolated yield
1	 **3b**	 **4b**	**1a**	3 h	100%
2			PPh_3	3 h	80%[b]
3	 **3c**	 **4c**	**1a**	1 h	100%
4			PPh_3	1.5 h	23%[b]
5	 **7a**	 **8a**	**1a**	20 min	75%
6			PPh_3	20 min	9%[b, c]
7			PPh_3	5 h	73%
8	 **7b**	 **8b**	**1a**	10 min	94%
9			PPh_3	10 min	90%
10	 **7c**	 **8c**	**1a**	15 min	75%
11			PPh_3	15 min	9%[b, c]
12			PPh_3	22 h	40%[b]

[a] Conditions: 1 mol % Au, 0.4 mmol alkyne, CH_2Cl_2 (1 mL for entries 1−4; 20 mL for entries 5−7 and 10−12; 4 mL for entries 8 and 9), 25 °C. Conversion of alkyne was 100% except for entries 2, 4, 6, and 11−12. [b] Starting material remained. [c] Conversion of **7** determined by ^{1}H NMR.

rate enhancement (13%, 1.5 h, entry 9) but to a much smaller extent than **1a** and **1b**. These results clearly indicate that the meta substituents (*t*-Bu and Me_3Si) of **1a** and **1b** play a critical role in promotion of cyclization.

The gold complex (**2a**, 1 mol %) with the holey ligand (**1a**) was applied to the cyclization of other acetylenic substrates and was compared with the PPh_3 complex in terms of catalytic activity (Table 2). In accordance with our assumption in the ligand design, the catalytic benefit of **1a** was significantly diminished in the reaction of cyclic substrate **3b**, which is programmed for cyclization via insertion of a ring between the alkyne and keto ester moieties (Table 2, entries 1 and 2).[9] Thus, only in the case of PPh_3 was a significant rate enhancement observed when compared to the reaction of acyclic substrate **3a** (Table 1, entry 2 vs Table 2, entry 2).

The superior performance of **1a** over PPh_3 recovered reasonably in the 7-*exo-dig* cyclization of linear acetylenic ketoester **3c** (Table 2, entries 3 and 4). The catalysis of **3c** cyclization by **2a** was completed in 1 h to afford an isomeric mixture of seven-membered ring compounds, consisting of a typical exomethylene compound, an α,β-unsaturated keto ester, and their enol forms. After base-catalyzed isomerization, the conjugated compound **4c** and its enol form were isolated in 65 and 35% yields, respectively (entry 3). When PPh_3 was used as a ligand, the reaction of **3c** showed only 23% conversion after 1.5 h (entry 4).

We next examined the gold(I)-catalyzed cycloisomerization of 1,7-enynes,[12,13] and found that the holey phosphine (**1a**) could assist cyclization more successfully than PPh_3 (Table 2, entries 5−12). Thus, the reaction of 1,7-enyne **7a** (0.02 M), which bears a malonate group at the bishomopropargyl position, with **1a** was completed in 20 min to afford **8a** in 75% yield, while the reaction with PPh_3 exerted only 9% conversion at 20 min and required 5 h for completion (entries 5−7). It should be noted that the cycloisomerization of **7a** was accompanied by formation of oligomeric compounds, and this could not completely be avoided even using **1a**.

To our surprise, the reaction of 1,7-enyne (**7b**) (0.1 M) bearing a malonate group at the homopropargyl position proceeded very rapidly irrespective of using either **1a** or PPh_3, being completed in 10 min to afford **8b** (as an isomer mixture) in high yields (entries 8 and 9). Perhaps this means that the Thorpe−Ingold effect worked more efficiently for **7b** than for **7a**, and that the steric effect of the holey ligand did not operate efficiently in the reaction of the programmed substrate (**7b**), as in the case of cyclic keto ester **3b** (entries 1 and 2). Eliminating the Throe−Ingold effect through the replacement of the malonate linker of **7b** with an ethereal one resulted again in the recovery of the superiority of **1a** over PPh_3 (reactions of **7c**, entries 10−12).

The results obtained here support our speculation that the cavity in the ligand forces the nucleophilic center (enol or alkene) close to the gold-activated alkyne, making ring-closing anti attack feasible. Although confirmation of this speculation must await further synthetic and mechanistic studies, we believe that the present work provides a general approach toward molecular design of efficient metal catalysts for the construction of cyclic structures. The holey triethynylphosphines are easy to synthesize and handle and are useful items for the toolbox in catalytic organometallic chemistry.

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Supporting Information Available: Experimental procedures for the synthesis of **1** and the cyclizations of **3** and **7** and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For P-coordination of alkynylphosphines, see: (a) Bardají, M.; de la Cruz, M. T.; Jones, P. G.; Laguna, A.; Martínez, J.; Villacampa, M. D. *Inorg. Chim. Acta* **2005**, *358*, 1365−1372. (b) Lauattani, E. L.; Lledós, A.; Suades, J.; Alvarez-Larena, A.; Piniella, J. F. *Organometallics* **1995**, *14*, 1053−1060. (c) Mague, J. T.; Mitchener, J. P. *Inorg. Chem.* **1969**, *8*, 119−125.

(2) For reactivity of alkynylphosphines, see: (a) Borkent, G.; Drenth, W. *Recueil* **1970**, *89*, 1057−1067. (b) Märkl, G.; Baier, H.; Liebl, R. *Synthesis* **1977**, 842−845. (c) Carty, A.; Jacobson, S. E.; Simpson, R. T.; Taylor, N. J. *J. Am. Chem. Soc.* **1975**, *97*, 7254−7262. (d) Liu, X.; Ong, T. K. W.; Selvaratnam, S.; Vittal, J. J.; White, A. J. P.; Williams, D. J.; Leung, P.-H. *J. Organomet. Chem.* **2002**, *634*−*635*, 4−11. (e) Johnson, D. K.; Rukachaisirikul, T.; Sun, Y.; Taylor, N. J.; Canty, J.; Carty, A. J. *Inorg. Chem.* **1993**, *32*, 5544−5552.

(3) For multinuclear complexes, see: (a) Ara, I.; Falvello, L. R.; Fernández, S.; Forniés, J.; Lalinde, E.; Martin, A.; Moreno, M. T. *Organometallics* **1997**, *16*, 5923−5937. (b) Berenguer, J. R.; Bernechea, M.; Forniés, J.; Gómez, J.; Lalinde, E. *Organometallics* **2002**, *21*, 2314−2324.

(4) See Supporting Information for a 3D model of **1a**.

(5) For reviews concerning gold catalysis, see: (a) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200−203. (b) Hashimi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990−6993.

(6) For gold(I)-catalyzed cyclizations of acetylenic keto esters, see: (a) K.-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526−4527. (b) Staben, S. T.; K.-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350−5352. (c) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133−4136.

(7) For gold(I)-catalyzed enyne cycloisomerizations, see ref 6c and: N.-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cádenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402−2406.

(8) For Cu-catalyzed C−P coupling, see: Afanasiev, V. V.; Belestakaya, I. P.; Kazankova, M. A.; Efimova, I. V.; Antipin, M. U. *Synthesis* **2003**, 2835−2838.

(9) The 6-*exo-dig* cyclization transforming **3b** to **4b** (see Table 2) using [AuCl(PPh$_3$)]/AgOTf catalyst has been reported (ref 6a), but it was much slower than the related 5-*exo-dig* cyclizations, requiring catalyst loading as high as 5 mol % for complete conversion (18 h).

(10) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696.

(11) The donor power was estimated by DFT calculations taking the electrostatic potential minimum in the lone-pair region. Details will be reported elsewhere.

(12) To the best of our knowledge, the gold-catalyzed 6-*exo-dig* cyclization of 1,7-enyne has not been reported. For examples of six-membered ring formation via gold-catalyzed 6-*endo-dig* cyclization of 1,5-enynes, see: Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705−9710.

(13) Scattered examples of 6-*exo-dig* cyclizations of 1,7-enynes with non-gold(I) catalysts have been reported. See: (a) Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294−10295. (b) Nishizawa, M.; Yadav, V. K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 1609−1611.

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